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Management of Biliary Tract Stones in Heart Transplant Patients

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Objective
The authors report their experience with biliary tract stones in adult and pediatric heart transplant patients, and review the current literature relative to this problem.

Summary Background Data
Prior studies in adults have noted that heart transplant patients frequently have cholelithiasis, but offer no consensus about treatment strategy. Few studies exist for pediatric heart transplant patients. A higher rate of hemolysis and cyclosporine-induced changes in bile metabolism may contribute to lithogenesis in this population.

Methods
A chart review was conducted for 211 patients who had heart transplants between January 1988 and September 1994 to determine prevalence of biliary tract stones, management strategies used, and outcome.

Results
Of 175 long-term heart transplant survivors, 52 (29.7%) had stones detected: 32.8% of adults (47/143) and 15.6% of children (5/32). The majority of patients (31) were diagnosed 4 months (mean) after transplantation; cholelithiasis developed in 10 of these patients (32%) within 11 months (median) after a negative ultrasound. Symptoms developed in 45% of patients. All patients underwent either elective (36) or urgent (6) cholecystectomy via an open (32) or laparoscopic (10) approach, or endoscopy for common bile duct stones (2). There were no deaths or complications during a follow-up period of up to 7 years.

Conclusion
Heart transplant patients have a high prevalence of symptomatic biliary tract stone disease. They can be treated safely via an open or laparoscopic approach after transplantation. The authors recommend routine gallbladder ultrasound screening and elective cholecystectomy in the post-transplant period if stones are detected.

With improvements in the prevention and treatment of tissue rejection, the population of patients who have successfully undergone cardiac transplantation has grown. Because these patients require continuous immunosuppression, they are susceptible to life-threatening medical and surgical problems, not only in the perioperative period but also during long-term follow-up after transplantation.

Biliary tract disease appears to be one of the more common complications requiring surgical management in the heart transplant patient.[1,2] The spectrum of problems ranges from asymptomatic cholelithiasis to fulmi-

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nant cholecystitis, cholangitis, and gallstone pancreatitis. Applying the same standards of management that exist for the normal population of patients with gallstones may not be appropriate. Considerations about the underlying cardiac status and the risks of higher morbidity in an immunosuppressed state are important, and may urge that treatment be administered at a different stage of disease than in the general population.

Not surprisingly, several studies on adult heart transplant patients with cholelithiasis have yielded a range of recommendations, without an accepted consensus on treatment strategy.[1-7] Only one published review addresses the problem of cholelithiasis specifically in pediatric heart transplant patients.[8]

However, the prevalence of cholelithiasis is considerably higher in heart transplant patients. Reports document a prevalence rate as high as 30% to 40% in adults[6,9] and 6.7% in children.[8] This increased prevalence has in part been attributed to cyclosporine, the main component of the immunosuppressive regimen for heart transplant patients.[3,8,9] Cyclosporine is a lipophilic endecapeptide that is metabolized in the liver and excreted in bile. It is known to have high hepatotoxicity and nephrotoxicity.[10] Experimental studies also have demonstrated that cyclosporine has effects on bile composition and serum lipid profile that may enhance gallstone formation.[11-14]

In the present study, we examined our experience with adult and pediatric heart transplant patients to determine the prevalence and consequences of biliary tract disease, the management strategies that were used, and the short- and long-term results of our treatment protocol. We summarize the current literature on this topic, including the experimental work on cyclosporine, and make recommendations about management of biliary stones in the heart transplant population.

METHODS

We reviewed the records of 211 patients at Emory University Hospital and Egleston Children's Hospital who had undergone heart transplantation between January 1988 and September 1994. Of these, 175 long-term survivors were identified for further study.

The study population consisted of 143 adults and 32 children. The immunosuppressive regimen used was mainly triple-drug therapy with cyclosporine, azathioprine, and steroids. Some patients received combinations of cyclosporine and azathioprine or cyclosporine and prednisone. The average cyclosporine dose used in adults was 4.4 ± 1.6 mg/kg per day and in children was 11.3 ± 3 mg/kg per day.

The clinical details analyzed included demographic data, indications for heart transplant, clinical manifestations of biliary tract disease, reason for surgery, type of biliary surgery, pathologic description of the surgical specimen, length of stay, and complications related to biliary surgery. Serum levels of total bilirubin, cholesterol, alkaline phosphatase, liver transaminases, amylase, and creatinine at the time of biliary surgery were noted.

Table 1. CLINICAL CHARACTERISTICS OF PEDIATRIC HEART TRANSPLANT PATIENTS WITH CHOLELITHIASIS

Parameter	Value*
No. heart Txp survivors	32
No. with cholelithiasis	5
Prevalence	15.6%
Age at heart Txp	8.4 yrs
Age at cholecystectomy	10.1 yrs
Main indication for heart Txp	Congenital heart disease (100%)
CyA dose	11.3 mg/kg/day
Cholecystectomy	
Open/laparoscopic	4/1
Elective/urgent	4/1
No. with biliary disease symptoms	3
Time from Txp to onset of symptoms	8 mos
Type of stone	
Mixed	1
Black	2
Brown	1
Length of hospital stay	3.6 days
Complications/deaths	None

Txp = transplant; CyA = cyclosporine
* Mean values are given unless otherwise indicated

Ultrasonographic examination of the gallbladder was the main diagnostic modality used. Routine ultrasonography of the gallbladder became part of the cardiac transplant program midway through the designated study years, and was ideally performed in the immediate post-transplant period as a baseline study. Surveillance was continued with annual ultrasound studies. The patients' medical records and radiology department records also were reviewed to identify any pretransplant ultrasonography studies.

RESULTS

Of the 175 long-term heart transplant survivors, 52 (29.7%) had biliary stones detected—47 of 143 adults (32.8%) and 5 of 32 children (15.6%). The population of patients with stones consisted of 38 males and 14 females, ranging in age from 4.5 to 69 years. The median age of the children was 10 years (range, 4.5–15 years) and that of adults was 53 years (range, 20–69 years).

In the pediatric group, all five patients had an orthotopic heart transplant performed for congenital heart disease. There were three boys and two girls; four of the

Table 2. CLINICAL CHARACTERISTICS OF ADULT HEART TRANSPLANT PATIENTS WITH BILIARY TRACT STONES

Parameter	Value*
No. heart Txp survivors	143
No. with biliary tract disease	47
Prevalence	32.8%
Age at heart Txp	51.8 yrs
Age at cholecystectomy	53 yrs
Main indication for heart Txp	Ischemic cardiomyopathy (62%)
CyA dose	4.4 mg/kg/day
Cholecystectomy	
Open/laparoscopic	28/9
Elective/urgent	32/5
Endoscopy for CBD stones	2
No. with biliary disease symptoms	17
Time from Txp to onset of symptoms	13.3 mos (mean) 11 mos (median)
Type of stone	
Mixed	12
Black	7
Yellow	7
Length of hospital stay	4.5 days
Complications/death	None

Txp = transplant; CyA = cyclosporine; CBD = common bile duct
* Mean values are given unless otherwise indicated

five patients were white. Table 1 summarizes their clinical information.

In the adult group, ischemic cardiomyopathy was the main indication (29 patients or 61.7%) for heart transplant, followed by idiopathic cardiomyopathy (15 patients or 31.9%). Forty-three patients had orthotopic heart transplants. There was one heart/lung transplant and three heterotropic heart transplants. There were 35 men and 12 women; 42 patients were white and 5 were black. Data for the adult heart transplant patients are found in Table 2.

Of the 52 patients with documented biliary disease, 8 had had a cholecystectomy in the remote past before heart transplantation. The other 44 patients had stones detected in the peritransplant period, and all underwent a definitive treatment procedure after the heart transplant procedure.

Asymptomatic cholelithiasis was diagnosed in two patients before heart transplantation. One was a 15-year-old boy in whom cholecystitis and pancreatitis developed 9 months after transplant who required urgent cholecystectomy. The other patient was a 55-year-old man in whom biliary colic and postprandial nausea developed 8 months after transplant who underwent elective cholecystectomy 2 months later.

Cholelithiasis was diagnosed in nine patients in the immediate post-transplant period. Presumably, they had asymptomatic cholelithiasis before the transplant. Thirty-one patients were diagnosed at a mean time of 4 months (range, 1–49 months) after transplant. Of these, ten (32%) had initial negative ultrasound results, which subsequently became positive within a median time of 11 months post-transplant.

The final two patients had prior cholecystectomies, but choledocholithiasis developed in the post-transplant period. Both patients had a heart transplant for ischemic cardiomyopathy. One patient (age 53 years) had intermittent episodes of diffuse abdominal pain with emesis 4 years after transplantation. The other (age 58 years) presented with symptoms of common bile duct obstruction 2 years after transplantation. Both were treated successfully by endoscopic removal of the common duct stones.

Forty-five percent of patients (20 of 44) became symptomatic within a median time of 11 months after the transplant (range, 2 months–4 years). Eighteen patients had repeated episodes of biliary colic, with variable severity of right upper quadrant pain, nausea, and vomiting. One patient had acute cholecystitis and pancreatitis, and one had clinical and laboratory findings of common bile duct obstruction (jaundice, elevated transaminases, and bilirubin). Of the 11 patients with known gallstones at the time of the transplant or immediately thereafter, 6 (55%) became symptomatic an average of 7.8 months after transplantation. Of the ten patients who initially had negative ultrasound results that subsequently became positive, four (40%) had symptoms within a mean of 10.5 months after the transplant.

No significant abnormalities in liver enzymes, amylase, bilirubin, or alkaline phosphatase levels were noted except in patients who had choledocholithiasis and pancreatitis. The average serum cholesterol level was 222 ± 39 mg/dL for adults and 165 ± 29 mg/dL for children (normal < 240 mg/dL). The average creatinine level was 1.7 ± 1.4 mg/dL for adults and 0.66 ± 0.23 mg/dL for children (normal 0.7–1.4 mg/dL).

Forty-two patients underwent cholecystectomy 2 to 51 months (mean 15 months) after transplantation. Thirty-six cholecystectomies were performed electively and six were done urgently. Thirty-two patients had standard open cholecystectomies. Cardiac biopsy was not obtained as a routine part of preoperative preparation. All children received preoperative antibiotics, usually a combination of ampicillin and gentamicin. The third-generation cephalosporin, ceftizoxime, was the most common antibiotic used in the 35 adult patients who received preoperative antibiotics. An intraoperative cholangiogram was performed routinely with open cholecystectomies and in three patients with laparoscopic cholecystectomies. They showed common bile duct dilation in two patients with chronic cholecystitis and no stones. There were no instances of intraoperative common bile duct exploration. A laparoscopic approach was used in

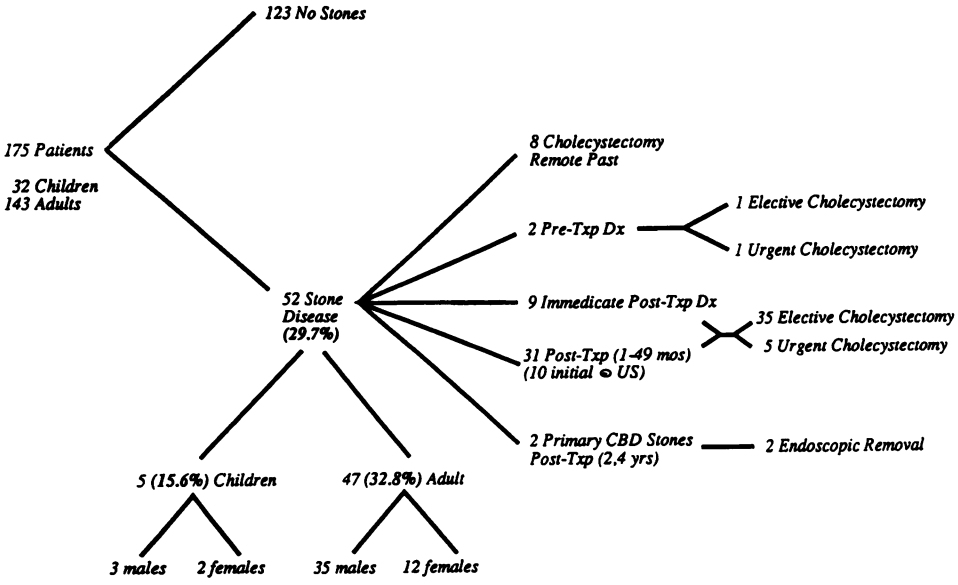

Figure 1. Summary of the current series of heart transplant patients with biliary tract stones.

ten patients, including a 4½-year-old boy. The average hospital stay after laparoscopic surgery was 2.9 days. Four other laparoscopic cholecystectomies were attempted but converted to open surgery secondary to poor visualization of anatomic structures. The patients tolerated both open and laparoscopic procedures well. There were no short-term complications in either group. The length of hospitalization was between 48 hours and 9 days (median 4 days). Two other patients had endoscopic removal of primary common bile duct stones (Fig. 1).

Records of pathologic examination of the gallbladder and its contents were available for 40 patients. Evidence of chronic cholecystitis was found in 30 patients (75%), acute cholecystitis in 2, and cholesterolosis in 6. The majority of stones were mixed (12), which described a stone consisting of a combination of bile pigments and cholesterol deposits. Yellow (8) and black (9) stones occurred with approximately equal frequency. There was one brown stone in the pediatric patient with cholecystitis and pancreatitis. Of the ten patients who developed new gallstone disease, five had yellow stones, two had black, one had mixed stones, one had chronic cholecystitis without stones, and information was unavailable for the last patient. Biochemical analysis of the stones was not performed.

The immunosuppressive regimen stayed essentially the same in the perioperative period as in the preoperative period. The only significant difference was that 62% of patients (26 of 44) received one additional stress dose of steroids on the day of surgery.

Clinical follow-up of patients in this study occurred over an average of 4 years, with some patients being seen as long as 7 years after transplant. During this time, the patients exhibited no further biliary tract problems, and they had either no cardiac rejection (81%) or very low-grade rejection (19%) that did not require additional immunosuppressive therapy. There were no deaths.

DISCUSSION

The group of patients described in our review represents the largest reported series of heart transplant patients who have been routinely evaluated and treated for biliary tract disease. Our data corroborate previous findings that the prevalence of biliary tract stones is significantly higher in heart transplant patients than in the general population.[3,6,9] The prevalence rate for adults (32.8%) in our series is two to three times higher than expected from epidemiologic data based on North American groups of the same age, gender, and race as our patients.[15] The rate for children (15.6%) in our study is higher than the rate found in a similar population of pediatric heart transplant patients (6.7%)[8] and profoundly different from the less than 1% prevalence rate of gallstones cited for the general pediatric population.[16]

Another important observation from our review is that nearly half of the heart transplant patients with gallstones became symptomatic. This included both those with cholelithiasis detected in the immediate peritransplant period and those who developed new stones after transplantation. This observation may be especially relevant when trying to resolve recommendations made by prior studies. Girardet et al.[6] reported gallstones in 13 of 33 (39%) heart transplant patients. Three occurred in the remote past, nine were found during pretransplant evaluation, and one developed in the post-transplant period. Five asymptomatic patients had pretransplant cholecystectomies, with excellent results. The other five had urgent or emergent biliary tract surgery for symptomatic

stone disease after transplantation; serious complications developed in four, and two died. This led the authors to recommend mandatory gallbladder surveillance and surgery for cholelithiasis before heart transplantation. However, none of their patients with known cholelithiasis had elective cholecystectomy after the heart transplant, as we are recommending.

Several other authors[2,4,5] have advocated prophylactic cholecystectomy for patients with cholelithiasis approximately 6 months after transplantation, allowing for some recovery time, or earlier, as warranted by the development of symptoms. Sekela et al.[4] found that symptoms of biliary tract disease developed in 50% of their patients before cholecystectomy was performed, as is the case in our series.

Steck et al.[3] and Colon et al.[1] favored elective cholecystectomy later than 6 months after transplantation, but only in symptomatic patients. Steck recommended close clinical follow-up and avoidance of surgery in the asymptomatic patients because the majority of them (82%) remained asymptomatic. For the same reason, mandatory screening for gallstones was viewed as unnecessary. His series of 159 patients identified a 29.6% prevalence rate for cholelithiasis. Of seven patients undergoing surgery for symptomatic cholelithiasis, three (43%) had severe postoperative complications requiring prolonged hospitalization (range, 14–75 days) for resolution. In the group described by Colon et al.,[1] all five patients with known gallstones before transplantation developed cholecystitis in the post-transplant period. Acalculous cholecystitis developed in four others. Five of these nine patients (56%) had either emergent[1] or elective[4] cholecystectomy, with good results.

Weinstein et al.[8] address the problem of cholecystitis specifically in pediatric heart transplant patients. In their large series of 90 patients, 6 patients were found to have cholelithiasis, which was confirmed by ultrasonography only after the manifestation of symptoms. The status of the biliary tract in the remaining patients was unknown. One of the six patients died after an emergent cholecystectomy. The authors advocate thorough evaluation of the biliary system before transplant and elective surgery for cholelithiasis detected after transplantation.

Data from our group of patients indicate that half of those patients who develop symptoms do so within the first year after transplant. The median time to development of symptoms was 11 months after heart transplantation. This is similar to the time frame reported by Sekela et al.[4] Ten patients who underwent elective cholecystectomy had previously exhibited symptoms of biliary tract disease. Six of the ten patients had onset of symptoms from 2 to 11 months after transplantation. This underscores the need for vigilance during the early stage of follow-up.

The accelerated natural history of cholelithiasis in heart transplant patients also is demonstrated in a recent study by Peterseim et al.[17] Symptoms developed in 58% of their patients with pretransplant asymptomatic gallstones within a mean of 2 years after transplantation. In 17% of their patients without gallstones, gallstones de novo developed within a mean of 1.8 years from the heart transplant. They contrast this accelerated natural history of biliary tract stone disease with that of the general population, in which only 18% of patients with gallstones develop symptoms after 15 years, and no serious complications occur by observing patients until they become symptomatic. Peterseim et al.[17] recommend elective cholecystectomy (laparoscopic) for heart transplant patients with asymptomatic biliary tract stones in the post-transplant period to eliminate the risk of severe complications from biliary tract disease in these immunosuppressed patients and also to simplify the evaluation of cholestatic jaundice, which occurred in all of their post-transplant patients from either cholelithiasis, cyclosporine toxicity, azathioprine toxicity, or Gilbert's disease.

Biliary surgery can be performed safely in heart transplant patients. We encountered no short- or long-term complication in either children or adults. Laparoscopic cholecystectomy was tolerated well and is being used more frequently in organ transplant patients.[7,17–19]

In light of our findings and consideration of clinical patterns described by the previous authors, it would seem reasonable to adopt the following management strategy (Fig. 2). Screening for biliary tract disease seems to be prudent and useful because it is a means to identify those heart transplant patients who are at higher risk of developing biliary complications. We recommend routine biliary tract ultrasonography in all patients as part of their pretransplant evaluation and post-transplant surveillance. We also favor elective cholecystectomy or biliary tract endoscopy in all post-transplant patients in whom stones are identified. The main goal of this approach is to avoid the development of serious complications, such as cholecystitis and cholangitis, and also to avoid surgery under urgent and emergent circumstances, both of which seem to be associated quite consistently with greater morbidity and mortality.[2–4,6–8,18]

Apart from the clinical implications of biliary disease in heart transplant patients, its association with cyclosporine has been investigated in several animal models and clinical studies. It was observed that renal transplant patients treated with cyclosporine had elevated hepatic enzymes and developed gallstones, but those treated with azathioprine and steroids did not.[20] When the dose of cyclosporine was decreased in renal transplant patients who showed signs of hepatotoxicity, their symptoms improved.[21] Spes et al.[9] carried over the same observations to heart transplant recipients and related increased serum cyclosporine levels measured in the early postoper-

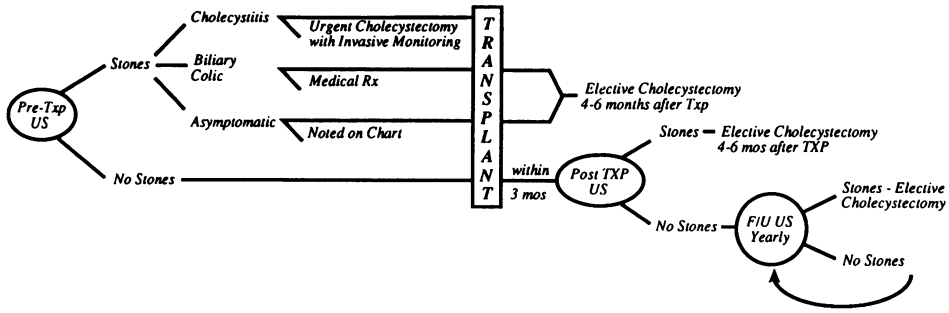

Figure 2. Proposed management protocol for heart transplant patients with biliary tract stones.

ative period to the high incidence of gallstones that developed in their patients. These studies suggested that the toxic side effect of cyclosporine on the liver could predispose to gallstone formation.

Experimental work in small animal models found cyclosporine to cause cholestasis as well. These studies showed a significant decrease in bile flow and bile salt secretion in cyclosporine-treated rats and pigs without changes in biliary cholesterol and phospholipid.[11,12] A proposed mechanism for this effect of cyclosporine is perturbation of the hepatocyte membrane by a lipophilic compound such as cyclosporine.[11,12] However, Queneau et al.[22] demonstrated that cholestasis in cyclosporine-treated rats can be improved by taurodeoxycholate, a conjugate of the hydrophilic bile acid ursodeoxycholate, which has choleretic properties.

Other studies describe the changes in serum lipid profile after cyclosporine treatment. Ballantyne et al.[13] showed total cholesterol and low-density lipoprotein cholesterol levels increased by 21% and 31%, respectively, in patients receiving cyclosporine for amyotrophic lateral sclerosis. Edwards et al.[14] demonstrated similar changes after only 3 months of treating psoriasis patients with cyclosporine, and found that they are reversible when cyclosporine is stopped.

The final common effect of these cyclosporine-induced changes presumably is to alter the balance in bile composition to favor stone formation.[23] Factors other than cyclosporine may contribute to gallstone formation in heart transplant patients. These may explain why cholesterol stones are not the predominant type of gallstone found in this population. In our study and those of others,[5,6] mixed stones were found most frequently. Gallbladder stasis, a known risk factor for cholelithiasis, could be a factor because many of the patients are extremely ill for a substantial period of time before the transplant. An association between ischemic cardiomyopathy from atherosclerotic coronary artery disease and cholesterol cholelithiasis has long been postulated but has not been proven. Rapid fluctuation in body weight, either obesity or marked weight loss, is another possible risk factor for the development of cholelithiasis.[3] Pretransplant liver congestion from cardiac failure, common in this patient population, increases cyclosporine's hepatotoxic effect and thus, the lithogenicity of the bile.[8] Finally, chronic hemolysis from any cause will lead to formation of black pigment gallstones.[23] A higher rate of hemolysis in our patients, either from underlying heart disease or from multiple prior surgeries, especially in children with congenital heart defects, may be another factor. Our review was not designed to address these questions in detail, but points to the likely multifactorial etiology of gallstones in heart transplant patients (Figs. 3 and 4).

We conclude from the observations in our series of patients and from current literature that biliary tract stone disease in heart transplant patients is a common problem that, in this group of patients, does not have a benign natu-

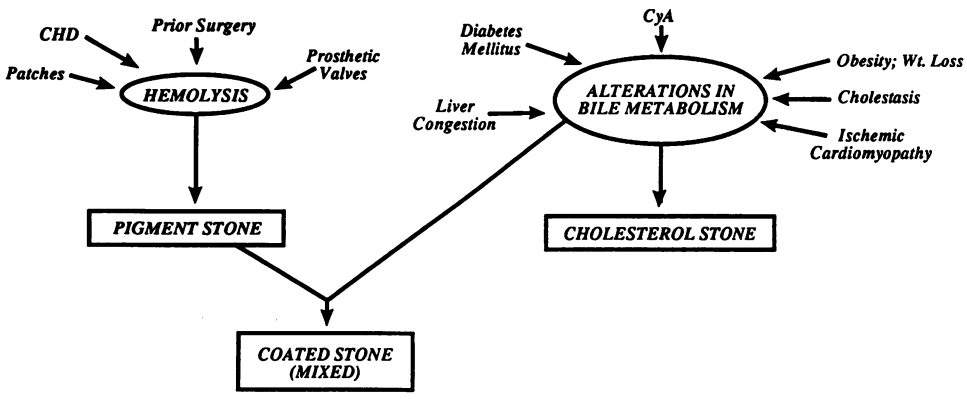

Figure 3. Multifactorial etiology of gallstones in heart transplant patients.

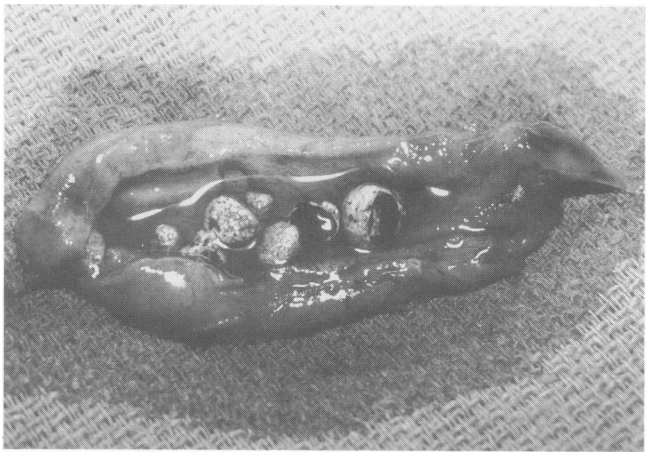

Figure 4. Example of a "coated" or "mixed" gallstone from a pediatric heart transplant patient who underwent cholecystectomy. The black core is composed of breakdown products of bilirubin and it is covered by cholesterol deposits.

ral course. Available surgical treatments, namely cholecystectomy and endoscopy, are tolerated well by heart transplant patients after transplantation. Recognition of such observations is important for physicians who follow these patients in the setting of the heart transplant center, and especially for general surgeons and other physicians who are increasingly involved with their care in community-based practices. Awareness of which patients are at higher risk—*e.g.*, through routine screening and early recognition of symptoms when they develop—will help initiate prompt and effective treatment.

Acknowledgments

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Discussion

DR. JOAQUIN S. ALDRETE (Birmingham, Alabama): Dr. Thompson, Dr. Copeland, Members, and Guests. I wish to express my appreciation to Dr. Amerson and Dr. Ricketts for inviting me to discuss this important contribution and for making their manuscript available to me several weeks ahead of the meeting.

They have carefully analyzed a field that has been emerging in the past 10 years. As more heart transplants have been done and these patients have survived longer periods of time, it has become evident that they have a number of illnesses affecting their digestive system. Some of them with presentation, incidence, and evolutions that are quite different from the nontransplant population and, in fact, different, I think, from patients similarly immunosuppressed because of kidney or liver transplants.